25265-71-8

DRAFT REPORT

SUPPORT FOR CHEMICAL NOMINATION AND SELECTION PROCESS OF THE NATIONAL TOXICOLOGY PROGRAM

NIEHS CONTRACT No. NO1-ES-5-5097

EXECUTIVE SUMMARY OF DATA

DIPROPYLENE GLYCOL

November 30, 1987

Rev. September 9, 1988

Submitted to:

National Toxicology Program
National Institutes of Health
Building 31, Room 2B-55
Bethesda, Maryland 20892

Submitted by:

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LIST OF ENCLOSURES

DIPROPYLENE GLYCOL*

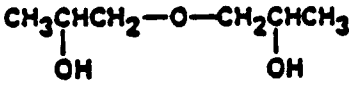
I. Chemical and Physical Information

A. Synonyms: Propanol, oxybis-
1,1'-Oxybis(2-propanol)
2,2'-Oxybis(1-propanol)
2-(2-Hydroxypropoxy)-1-propanol
Di-1,2-propylene glycol
2-Propanol, 1,1'-oxybis-
1-Propanol, 2,2'-oxybis-
DPG

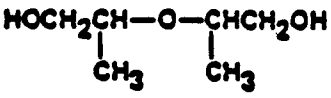
B. CAS No.: 25265-71-8 (Isomeric mixture)

C. Molecular Formula: $C_6H_{14}O_3$

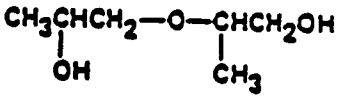
C. Structural Formulas:



110-98-5
1,1'-Oxybis(2-propanol)
43%



108-61-2
2,2'-Oxybis(1-propanol)
4%



106-62-7
2-(2-Hydroxypropoxy)-1-propanol
53%

E. Molecular Weight: 134.18

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*The National Cancer Institute has nominated dipropylene glycol for subchronic studies, metabolism, mutagenicity, teratogenicity and hematological effects.

November 30, 1987, rev. September 9, 1988

F. Physical Properties:

1. Physical State: Colorless and slightly viscous liquid (Hawley, 1981)
2. Melting Point: -40°C, pour point (Kirk-Othmer, 1980)
3. Boiling Point: 229-232°C (Cosmetic Ingredient Review, CIR, 1985); 233°C (Hawley, 1981)
4. Flash Point: 250-280°F (Browning, 1965); 280°F (137.7°C) (Hawley, 1981); 118°C (closed cup), (Kirk-Othmer, 1980)
5. Vapor Pressure: 0.01 mm of Hg at 20°C (Hawley, 1981)
6. Specific Gravity: 1.0252 at 20°C referred to water at 20°C (Hawley, 1981)
7. Refractive Index: 1.439 (CIR, 1985)
8. Solubility in Water: Soluble (Hawley, 1981); miscible (Browning, 1985)
9. Solubility in Organic Solvents: Soluble in methanol and ether (Browning, 1965); alcohol and acetone (CIR, 1985); toluene (Hawley, 1981)
10. Log Octanol/Water Partition Coefficient: No information was found.
11. Other: Viscosity: 107 poise (20°C); coefficient of expansion: 0.00073 (20°C); combustible (Hawley, 1981)

II. Production/Use/Exposure/Environmental/Regulatory Data

A. Production

1. Manufacturing Process

Dipropylene glycol (DPG) is produced commercially as a co-product with propylene glycol by hydration of propylene oxide. DPG can also be prepared by the reaction of propylene glycol with propylene oxide (Kirk-Othmer, 1980; CEH, 1984).

2. Volume

The public portion of the Toxic Substances Control Act (TSCA) Chemical Substance Inventory (TSCA Inventory) reported domestic production of DPG of between 32.0 and 170 million pounds in 1977 as indicated in Table 1 (USEPA, 1987; refer to Enclosure 1). Of the seven manufacturers indicated in the TSCA Inventory, one was not identified, one reported zero production in 1977, and one did not report production data for its two sites.

The Chemical Economics Handbook (CEH) and the U.S. International Trade Commission (USITC) reported U.S. production data for DPG for the years 1980 through 1985 (Table 1). Annual production volume ranged from 27.1 to 52.9 million pounds, with the highest volume reported in 1985.

The TSCA Inventory reported the import of DPG in 1977 as indicated in Table 1 (USEPA, 1987; refer to Enclosure 1). The volume reported (Table 1) was imported by two companies; three companies did not report import volume for 1977.

No import data for DPG were reported by the USITC (1982b-1984b), CEH (1984), or the U.S. Department of Commerce (USDOC, 1984-1986).

3. Producers and Importers

Producers

The following companies were listed as manufacturers of DPG:

Atlantic Richfield Company (SRI International, 1986)
Bayport, TX

Table 1. Production and Import Data for Dipropylene Glycol

Year	U.S. Production (millions of pounds)	Import	Reference
1977	32.0-170	0-0.002	USEPA (1987)
1980	27.1	ND[a]	CEH (1984)
1981	46.7	ND	CEH (1984)
	46.7	ND	USITC (1982a)
1982	39.1	ND	CEH (1984)
	39.1	ND	USITC (1983a)
1983	41.7	ND	CEH (1986)
	41.7	ND	USITC (1984a)
1984	48.1	ND	CEH (1984)
	48.1	ND	USITC (1985)
1985	52.9	ND	USITC (1986)

[a]ND = No data were reported.

Dow Chemical Company U.S.A. Freeport, TX Plaquemine, LA	(SRI International, 1986; USEPA, 1987)
Givaudan Corporation Clifton, NJ	(USEPA, 1987)
Jefferson Chemical Company, Inc. Austin, TX Port Neches, TX	(USEPA, 1987)
March Chemical Company, Inc. Denham Springs, LA	(USEPA, 1987)
Olin Corporation Brandenburg, KY	(SRI International, 1986; USEPA, 1987)
Oxirane Chemical Company Pasadena, TX	(USEPA, 1987)
Texaco, Inc. Port Neches, TX	(SRI International, 1986)
Union Carbide Corporation South Charleston, WV	(SRI International, 1986)

Importers

The following companies were listed as importers of DPG (USEPA, 1987):

ICI Americas, Inc.
Wilmington, DE

JPM Imports, Inc.
Astoria, NY

Roure Bertrand DuPont, Inc.
Teaneck, NJ

Synarome Corporation
New York, NY

V. Mane Fils, Inc.
Fairfield, NJ

4. Technical Product Composition

Commercial DPG is composed of three isomers: 2-(2-hydroxypropoxy)-1-propanol, 53%; 1,1'-oxybis(2-propanol), 43%; and 2,2'-oxybis(1-propanol), 4% (Kirk-Othmer, 1980).

B. Use

The Chemical Marketing Reporter (CMR) listed the following use patterns for DPG, expressed as percentages of total DPG production volume: as an intermediate for the production of polyester resins (60%) and alkyd resins (7%); as a plasticizer (25%); and as a hydrocarbon extractive solvent, for urethane polyol production, and other uses (8%) (CMR, 1984). DPG has been reported as an ingredient in 50 cosmetic formulations in concentrations ranging from under 0.1 percent to 50 percent. It is utilized in hair care and bath products, perfumes, facial makeup, deodorants, and skin care preparations (CIR, 1985).

C. Occupational Exposure

The National Occupational Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1972 to 1974, estimated that 227,892 workers in 24,619 plants were potentially exposed to DPG in the workplace (NIOSH, 1976). The estimates were derived from observations of the actual use of DPG (12% of total estimate), the use of tradename products known to contain DPG (63%), and the use of generic products suspected of containing the compound (25%). The largest numbers of exposed workers were in the medical and other health services, wholesale trade, chemicals and allied products, automotive dealers and service stations, and primary metal industries (refer to Enclosure 2). The occupational groups with the largest numbers of exposed workers were automobile mechanics, machine operatives (miscellaneous specified), registered nurses, and janitors and sextons (refer to Enclosure 3).

Preliminary data from a second workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, indicated that 8,084 workers, including 835 women, at 108 sites were potentially exposed to DPG in the workplace in 1980 (NIOSH, 1984). The largest numbers of exposed workers were in the chemicals and allied products industries (refer to Enclosure 4). The occupational groups with the largest numbers of exposed workers were chemical technicians, mixing and blending operators, and janitors and cleaners (refer to Enclosure 5). Unlike NOHS, the NOES estimates were based only on direct observation by the surveyor of the actual use of the compound.

Neither the NOHS nor the NOES database contains information on the frequency, level or duration of exposure of workers to any of the chemicals listed therein. They are surveys that only provide estimates of workers potentially exposed to the chemicals.

The NIOSH Tradename Ingredient Data Base of NOHS listed DPG as a constituent of 129 products used in industrial applications (NIOSH, 1976). The concentration of DPG in the products ranged from 1 to 99%, with 93 products containing 1-10%, 23 containing 11-50%, 3 containing 51-60%, and 10 containing 61-99% DPG.

The American Conference of Governmental Industrial Hygienists has not adopted a threshold limit value for DPG (ACGIH, 1986).

D. Consumer Exposure

DPG is listed in the U.S. Consumer Product Safety Commission's Chemicals in Products database as being used in air/room fresheners and household cleaners. This database, however, was compiled approximately 10 years ago and has not been updated. The presence of DPG in current consumer products has not subsequently been verified (USCPSC, 1987).

As noted above, DPG is used in cosmetic formulations at concentrations ranging from less than 0.1 percent to 50 percent (CIR, 1985).

E. Environmental Data

No information was found on the releases or ambient environmental concentrations of DPG.

F. Regulatory Status

The Occupational Safety and Health Administration has not established a permissible exposure limit for DPG (OSHA, 1983).

DPG was scored for exposure potential and biological effects in 1980 by the TSCA Interagency Testing Committee (ITC) (ITS, 1985). The ITC reviews chemicals in commerce for potential referral to the Environmental Protection Agency for consideration for industry-required testing for toxicological and/or environmental effects. DPG was not selected for further study by the ITC as a result of the scoring activity.

The Food and Drug Administration has approved DPG as a component of adhesives intended for use in packaging, transporting, or holding food; as a defoaming agent used as components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting or holding food; and as a surface lubricant employed in the manufacture of metallic articles that contact food (FDA, 1986).

No other Federal regulations relating to DPG were found.

III. Toxicological Effects

A. Human Data

1. Acute: Gosselin et al. (1984) rated DPG as a slightly toxic compound with a probable lethal dose for humans of 5 to 15 g/kg.

   Mild irritation was reported for 6 of 101 subjects after the first exposure to a shaving preparation containing 7.2% DPG in the Schwartz-Peck prophetic closed (48-hour) patch test. When this test was repeated 2 weeks later, eight subjects had mild irritation. Open patch (48-hour) tests and subsequent ultraviolet (UV) exposure produced no reactions (CIR, 1985).

   "Mild irritation with probable fatiguing" but neither sensitization nor photosensitization was reported following the exposure of 50 volunteers to the shaving preparation in the Draize-Shelanski repeated insult patch test. No reactions were observed in 59 subjects who used the shaving preparation in a 4-week controlled use test (CIR, 1985).

   No irritation or sensitization reactions were produced in human volunteers exposed for 48-hours to 20% DPG in petrolatum in a closed patch test (Epstein, 1974, as cited in Opdyke, 1978).

2. Epidemiological Evidence/Case Reports: No information was found.

3. Chemical Disposition: No information was found.

4. Biochemical Effects: No information was found.

5. Carcinogenicity/Chronic: No information was found.

6. Teratogenicity and Reproductive Effects: No information was found.

B. Animal Data

1. Acute: The LD_{50} data for DPG are reported in Table 2. In the rat, narcosis was induced by lethal intraperitoneal (ip) doses of DPG (Shaffer, 1951).

Slight renal tubular degeneration was noted in the kidneys of mice (Carworth Farms, females) 1 to 4 days following a single ip injection of 4.5 g/kg DPG. Five to seven days after dosing, hyperactive mitosis was detected in the spleen, intestinal mucosa, liver, and lymphoid tissue (Karel et al., 1947).

Two of ten rabbits (strain not specified) that were injected intravenously with DPG (2 to 4 cc/kg body weight) died 4 days after treatment. Kidney lesions were detected in both of these animals. The remaining eight rabbits were sacrificed between study days 1 and 21. Lesions were detected in the kidneys of three of these animals. The kidney lesions were characterized by extensive hydropic degeneration of the renal epithelium. Occasionally, hemoglobin-containing casts were observed in the collecting tubules (Kesten et al., 1939).

Negligible irritation was produced by the repeated application (10 applications in 12 days) of DPG (concentration not reported) to the skin of rabbits (strain, sex, and number not specified) (Rowe and Wolf, 1982).

Application of 510 mg of undiluted DPG caused irritation of the eye in the rabbit (strain, sex and number not specified); a product formulation containing 7.2% DPG produced minimal, transient irritation (CIR, 1985).

Table 2. Acute Toxicity of DPG in Laboratory Animals

Species	Strain	Route	No/Sex/ Dose Level	LD_{50}	Reference
Mouse	--[a]	Orl	-/-	4.6 g/kg	Spector (1955, as cited in Opdyke, 1978)
Mouse	Carworth Farms	Ipr	≥ 6/F	4.5 ± 0.52 g/kg	Karel et al. (1947)
Mouse	--	Ipr	-/-	4.6 g/kg	CIR (1985)
Rat	Sherman	Orl	5/M	14.85 g/kg (10.65-20.72)[b]	Shaffer et al. (1951)
Rat	--	Orl	-/-	14.8 mL/kg	Kirk-Othmer (1980)
Rat	--	Orl	-/-	15 g/kg	CIR (1985)
Rat	Sherman	Ipr	5/M	10.59 g/kg (5.94-17.93)[b]	Shaffer et al. (1951)
Rat	--	Ipr	-/-	10 g/kg	CIR (1985)
Rat	Sherman	Ivn	5/M	5.8 g/kg	Shaffer et al. (1951)
Rat	--	Ivn	-/-	5.8 g/kg	CIR (1985)
Rabbit	--	Dermal	-/-	>5 g/kg	Moreno (1974, as cited in Opdyke, 1978)
Rabbit	--	Dermal	-/-	>20 mL/kg	Deichmann (1979)
Rabbit	--	Dermal	-/-	20 mL/kg	Kirk-Othmer (1980)
Dog	--	Ivn	-/-	11.5 g/kg	Hanzlik et al. (1939)

[a]Information not provided.

[b]95% confidence limits.

2. Chemical Disposition: When dogs (breed, number, and sex not specified) were given 5 mL/kg of DPG intragastrically, the DPG disappeared from the blood in approximately 24 hours (Newman et al., 1940, as cited in Browning, 1965).

3. Biochemical Effects: No information was found.

4. Prechronic: A group of 25 rats (strain and sex not specified) was dosed with 10% DPG in drinking water over a period of 68 days. Seven of the rats died after 10 to 30 days of treatment; lesions were detected in the kidneys of 5 of these. Lesions were detected in the kidneys of 4 of the remaining 18 animals, which were killed at intervals from days 9 through 68 of treatment. No effect was detected in rats given 1 to 5% DPG in drinking water for 33 to 77 days (Kesten et al., 1939).

5. Carcinogenicity/Chronic: No information was found.

6. Teratogenicity and Reproductive Effects: No information was found.

C. Genotoxicity

No information was found.

D. Structure-Activity Relationships

1. Carcinogenicity

In a carcinogenicity bioassay, ethylene glycol monoethyl ether (EGEE) was administered by gavage to male and female B6C3F$_1$ mice and Fischer 344/N rats. At necropsy, an apparent enlargement of the adrenal glands in male rats was observed. EGEE interfered with the development of spontaneous gross

lesions of the spleen, pituitary gland, and testes, which commonly occurs in aging male Fischer 344/N rats, and caused a decrease in the incidences of enlarged spleens and pituitaries in males and females and of subcutaneous masses in the mammary gland region in aging female Fischer 344/N rats. Microscopic examination of the testes of male mice and rats revealed testicular atrophy. Histopathology review of this study is in progress (Melnick, 1984).

2. Reproductive Toxicity

Hardin (1983) reviewed the reproductive toxicity of glycol ethers. Ethylene glycol monomethyl ether (EGME), EGEE, and diethylene glycol monoethyl ether (diEGEE) induced adverse effects on the male reproductive system in four mammalian species: EGME in the mouse, rat, and rabbit; EGEE in the mouse, rat, and dog; and diEGEE in the mouse. Observations in various studies included testicular atrophy, degeneration of the germinal epithelium, infertility, and abnormal sperm-head morphology. Embryotoxicity and teratogenicity were demonstrated in mice and rats following treatment with EGME, and in rats and rabbits after EGEE administration. Significant findings in the fetuses were exencephaly and digital defects in mice, and cardiovascular malformations in rats and rabbits. Ethylene glycol monobutyl ether (EGBE) failed to cause testicular atrophy in mice, and was not embryotoxic or teratogenic in rats exposed by inhalation.

DPG has not previously been selected for testing by the National Toxicology Program (NTP CHEMTRACK, 1987).

The NTP testing status of compounds structurally related to DPG is summarized in Table 3.

Table 3. NTP Testing Status of Compounds Structurally Related to Dipropylene Glycol[a]

Chemical	CAS Number	Genotoxicity	Carcinogenicity	Other
Diethylene glycol	111-46-6	-Negative in Salmonella	--	-Short-term in vivo reproductive toxicity study completed -Continuous breeding study completed
Diethylene glycol monomethyl ether	111-77-3	--	--	-Short-term in vivo reproductive toxicity study completed -Conventional teratology study completed
Diethylene glycol monoethyl ether	111-90-0	--	--	-Short-term in vivo reproductive toxicity study completed -Conventional teratology study completed -Continuous breeding study completed
Diethylene glycol monobutyl ether	112-34-5	-Selected for Salmonella	--	-Two short-term in vivo reproductive toxicity studies completed
Ethylene glycol monomethyl ether	109-86-4	-On test in Salmonella	-Selected for inhalation study	-Short-term in vivo reproductive toxicity study completed -Two continuous breeding studies completed -Conventional teratology study completed
Ethylene glycol monoethyl ether	110-80-5	-Negative in Salmonella -Negative in mouse lymphoma assay -Negative for sex linked recessive lethal mutations and negative for reciprocal translocations in Drosophila -Positive for chromosomal aberrations and sister-chromatid exchanges in CHO cells	-Histopathology phase of chronic gavage bioassay in rats and mice -Selected for inhalation study	-Short-term in vivo reproductive toxicity study completed -Two dominant lethal studies completed -Two conventional teratology studies completed -Two inhalation teratology studies completed -Two continuous breeding studies completed -Spermhead morphology studies completed
Ethylene glycol monobutyl ether	111-76-2	-Negative in Salmonella -On test for chromosomal aberrations and sister-chromatid exchanges in CHO cells	-Selected for inhalation study	-Chemical disposition studies in progress -Short-term in vivo reproductive toxicity study completed -Conventional teratology study completed -Continuous breeding study completed

[a]NTP CHEMTRACK (1987).

IV. Nomination Source

A. Source: National Cancer Institute (NCI, 1986a, b)

B. Recommendations: Subchronic studies, metabolism, mutagenicity teratogenicity, and hematological effects

C. Rationale/Remarks:
- High production volume
- Limited toxicological data
- Lack of carcinogenicity test data
- Structural interest

D. Priority: High

E. Date of Nomination: February 1986

V. Chemical Evaluation Committee Review

A. Date of Review: July 29, 1987

B. Recommendations:
- Subchronic studies including emphasis on hematological effects
- Carcinogenicity
- Metabolism
- Mutagenicity studies of mixture of isomers
- Teratology screen

C. Priority: Moderate

D. NTP Chemical Selection Principles: 3, 8

E. Rationale/Remarks:
- High production
- Potential for human exposure
- Limited toxicology data
- Structural interest
- If mixture is mutagenic, test individual isomers

VI. Board of Scientific Counselors

A. Date of Review: December 15, 1987

B. Recommendations:
- Subchronic studies including emphasis on hematological effects
- Carcinogenicity
- Metabolism
- Teratology screen

C. Priority: Moderate

D. Rationale/Remarks: - High production
- Potential for human exposure
- Limited toxicology data
- Structural interest

VII. Executive Committee Review

A. Date of Review: January 27, 1988

B. Decision: Selected as a NTP Fiscal Year 1988 priority chemical for in-depth toxicological evaluation

VIII. Information Sources

This report was prepared by a multidisciplinary team of scientists and technicians. Dr. Y'Vonne R. Jones-Brown was the principal author.

The information resources used in preparing this review include the automated data bases listed below, journal articles, general reference materials, and contractor/agency reports.

ON-LINE DATA BASES SEARCHED

MEDLARS

CHEMLINE	
RTECS	
HSDB	
MEDLINE	1983-Present
TOXLINE	1966-Present
TOX 76	1976-1980
TOX 65	1940-1975
CANCERLIT	1963-Present
CANCERPROJ	1978-1981

DIALOG

BIOSIS PREVIEWS	1969-Present
CHEMICAL EXPOSURE	1974-Present
CIN (Chemical Indust. Notes)	1974-Present
CONFERENCE PAPERS INDEX	1973-Present
CRGS (Chemical Regulations and Guidelines System)	1982-Present
EMBASE	1974-Present

ENVIROLINE	1971-Present
ENVIRONMENTAL BIBLIOGRAPHY	1974-Present
FEDERAL REGISTER ABSTRACTS	1977-Present
FEDERAL RESEARCH IN PROGRESS	1976-Present
FSTA (Food Science and Technology Abstracts)	1969-Present
IPA (International Pharmaceutical Abstracts)	1970-Present
LIFE SCIENCES COLLECTION	1978-Present
NTIS	1970-Present
OCCUPATIONAL SAFETY AND HEALTH	1972-Present
PTS PROMT	1972-Present
POLLUTION ABSTRACTS	1970-Present
SCISEARCH	1974-Present

CIS

OHMTADS
CESARS, DERMAL, ENVIROFATE,
GENETOX, and ISHOW

BRS

KIRK-OTHMER	1978-Present

INFOLINE

LABORATORY HAZARD BULLETIN	1981-Present
CURRENT AWARENESS IN BIOLOGICAL SCIENCES	1983-Present
CHEMICAL HAZARDS IN INDUSTRY	1984-Present
WORLD SURFACE COATING ABSTRACTS	1976-Present

OTHERS

ITS
NOES
NOHS
NTP CHEMTRACK
STORET
TSCA INVENTORY

HAZARDLINE	1983-Present
CAS ONLINE	1967-Present